CCA-793

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Note

The Preparation and Isomerization of Some New 2,4,5-Trisubstituted 2-Imidazolines

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Received April 25, 1973

A number of *meso* 2,4,5-trisubstituted 2-imidazolines, obtained by cyclization of corresponding hydroamides have been isomerized to *racemic* 2,4,5-trisubstituted 2-imidazolines. The configuration of 2-furyl derivative was proved by resolution of *racemic* mixture.

In an attempt to prepare some new disubstituted derivatives of EDTA, we synthesized a number of 1,2-disubstituted ethylenediamines*. A useful method for the preparation of 1,2-diphenyl-ethylenediamine reported by Lifschitz and Bos[1] turned our attention to 2,4,5-trisubstituted 2-imidazolines.

It is known that the title compounds can be readily prepared by thermal cyclization of corresponding hydroamides. Several authors showed that »amarine« obtained by cyclization of hydrobenzamide is *meso*-, and »isoamarine« obtained by isomerization of amarine is (±)-2,4,5-triphenyl-2-imidazoline[2].

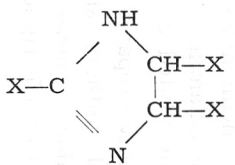
In this work we wish to report the preparation of several new *meso* and *racemic* 2,4,5-triaryl- and 2,4,5-tri(2-furyl)-2-imidazolines (Table I). Hydroamides, with the exception of 4-chloro-derivative have been reported earlier, and were prepared by the reaction of an aromatic or heteroaromatic aldehyde with a large excess of aqueous ammonia[3]. They were converted to corresponding *meso*- 2,4,5-trisubstituted 2-imidazolines by thermal cyclization in the presence of alkali[4], or without it[5].

There are several methods suitable to isomerize amarine to isoamarine[1,6], but only a few data about conversion of *meso*-2,4,5-tri(2-furyl)-2-imidazoline (furfurine) to *racemic* isomer (isofurfurine)[7,8]. We found that the best results could be obtained by the use of modified method reported by Basolo at al.[6a] By this method we prepared several hitherto unpublished *racemic* 2,4,5-trisubstituted 2-imidazolines (Table I) including isofurfurine which were a subject of controversy in the literature[7,8]. We showed that furfurine should be *meso*- and isofurfurine (±)-2,4,5-tri-(2-furyl)-2-imidazoline, as we successfully resolved the racemic mixture and obtained both, (+) and (—) enantiomers.

* Described in detail in the Ph. D. Thesis of Š. Zupanc, University of Zagreb, 1964.

TABLE I

2,4,5-Trisubstituted 2-imidazolines



No.	X	Config.	Method	Yield %	M. p./°C	Formula	Anal. % C	Calc'd found % H	Calc'd found % N
I	2-Cl—C_6H_4	*meso*	A	46	156—157	$C_{21}H_{15}Cl_3N_2$	62.79 62.49	3.76 3.61	6.97 7.00
II	4-Cl—C_6H_4	*meso*	A	68	186—188	$C_{21}H_{15}Cl_3N_2$	62.79 62.75	3.76 3.85	6.97 6.62
III	3-NO_2—C_6H_4	*meso*	A	66	266—268[a]	$C_{21}H_{16}ClN_5O_6$	53.68 53.58	3.43 3.56	14.57 14.80
IV	5-CH_3—C_4H_2O	*meso*	B	71	176—177[b]	$C_{24}H_{21}N_5O_{10}$	53.44 53.38	3.92 4.17	12.98 13.26
V	4-Cl—C_6H_4	*racem.*	C	89	199—200	$C_{21}H_{15}Cl_3N_2$	62.79 62.69	3.76 3.63	6.97 6.79
VI	3-NO_2—C_6H_4	*racem.*	C	72	173—174	$C_{21}H_{15}N_5O_6$	58.20 58.47	3.50 3.37	16.16 16.10
VII	5-CH_3—C_4H_2O	*racem.*	D	65	183—185	$C_{18}H_{18}N_2O_3$	69.67 69.40	5.85 5.92	9.03 8.88

EXPERIMENTAL*

4,4'4''-Trichlorohydrobenzamide

A mixture of 250 ml aqueous ammonia ($\gamma = 0.88$) and 42.2 g (0.3 mole) 4-chlorobenzaldehyde in 120 ml of ethanol was shaked efficiently during 4 h and left overnight. The product (35.3 g, 88%) was separated and recrystallized from ethanol; prisms, m. p. 88—90 °C.

Anal. $C_{21}H_{15}Cl_3N_2$ (401.74) calc'd.: C 62.79; H 3.76; N 6.97%
found: C 62.78; H 3.20; N 7.25%

General Procedure for the Preparation of meso-*2,4,5-Trisubstituted 2-Imidazolines (I—IV)*

Method A. Dried hydroamide (0.1 mole) was heated during 4—6 h at 130—160 °C. On cooling to about 70 °C the melt solidified and was dissolved in minimum amount of hot ethanol (40—70 ml). The hot solution was acidified with hydrochloric acid to pH = 2—3, cooled, and crystalline hydrochloride (70—75%) separated. To the solution of hydrochloride in a minimum amount of hot ethanol, an excess of aqueous ammonia ($\gamma = 0.91$) was added. In most cases the oily product soon crystallized. After a recrystallization from ethanol the products were sufficiently pure.

Method B. Into a 700 ml of hot 2.5% aqueous KOH, 0.05 mole of powdered hydroamide was added in small portions. Heating in a steam bath was continued for 10 additional minutes. The oily product which solidifies on cooling, was separated and converted to oxalate by treating with hot 5% aqueous oxalic acid. Crystalline oxalate (70—80%) was converted to free base by treating of warm water solution with aqueous ammonia. On cooling the crystalline or amorphous (IV) product was separated and recrystallized from hot water.

General Procedure for the Preparation of racemic *2,4,5-Trisubstituted 2-Imidazolines (V—VII)*

A suspension of *meso*-2,4,5-trisubstituted 2-imidazoline (II—IV, 0.1 mole) in 50 ml 10% solution of NaOH in water/diethylene glycol (1:5) was boiled under reflux for 1—2 h. For the isolation of the product two methods were used.

Method C. To the reaction mixture 150—200 ml of 15% acetic acid in ethanol was added. After a short boiling the solution was filtered and the product precipitated by careful addition of conc. aqueous ammonia. A sufficiently pure product was obtained by recrystallization from ethanol.

Method D. The reaction mixture was diluted with tenfold volume of water and separated product recrystallized from hot water.

(±)-2,4,5-Tri(2-furyl)-2-imidazoline

Prepared from 21.4 g (0.08 mole) *meso*-2,4,5-tri(2-furyl)-2-imidazoline[4] according to general procedure (Method D.). Yield, 11.5 g (53%), m. p. 141—2 °C (Lit.[7] m. p. 143 °C).

Resolution of (±)-2,4,5-Tri(2-furyl)-2-imidazoline

To the hot solution of 8.7 g (+)-10-camphorsulfonic acid in 800 ml water 10.0 g isofurfurine was added. On cooling of filtered hot solution to +5 °C, less soluble crystalline salt was separated. After repeated fractional recrystallizations from water pure salt melting at 260—261 °C, $[\alpha]_D^{20} + 248°$ ($c = 0.454$ in ethanol) was obtained. On addition of conc. aqueous ammonia to the solution of less soluble salt (+)-2,4,5--tri(2-furyl)-2-imidazoline was separated and after recrystallization form water melts at 139—140 °C; $[\alpha]_D^{20} = +272°$ ($c = 0.460$ in ethanol).

The mother liquor, left after separation of dextrorotatory salt, was evaporated under reduced presure and by repeated fractional recrystallizations of residue from water pure laevorotatory salt, m. p. 247—148 °C; $[\alpha]_D^{20} = -176°$ ($c = 0.422$ in ethanol)

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* The melting points are uncorrected.

was isolated. By treatment with aqueous ammonia and recrystallization from water (—)-2,4,5-tri(2-furyl)-2-imidazoline melting at 139—140 °C; $[\alpha]_D^{20} = -258^0$ ($c = 0.440$ in ethanol) was obtained.

Acknowledgement. We are indebted to late Prof. V. Hahn for suggesting the problem and for stimulating discussions in early stage of the work. The authors wish to thank Mrs. I. Guštak-Mašek for the microanalyses.

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IZVOD

Priprava i izomerizacija novih 2,4,5-trisupstituiranih 2-imidazolina

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Nekoliko novih *mezo*-2,4,5-trisupstituiranih 2-imidazolina, pripravljenih ciklizacijom odgovarajućih hidroamida, izomerizirano je u odgovarajuće racemične 2,4,5--trisupstituirane 2-imidazoline. Razlučivanjem »izofurfurina« u oba enantiomera pokazano je da se radi o racemičnom obliku 2,4,-5-tri(2-furil)-2-imidazolina.

ZAVOD ZA ORGANSKU KEMIJU
TEHNOLOŠKOG FAKULTETA
I
INSTITUT »RUĐER BOŠKOVIĆ«
ODJEL ORGANSKE KEMIJE I BIOKEMIJE

Primljeno 25. travnja 1973.